Clinical Medicine

The Pharmacology of Neonatal Resuscitation and Cardiopulmonary Intensive Care
Part I—Immediate Resuscitation

WILLIAM E. BENITZ, MD; LORRY R. FRANKEL, MD, and DAVID K. STEVENSON, MD, Stanford, California

Resuscitation of a neonate requires both immediate cardiopulmonary resuscitation and extended intensive care. Initial resuscitation of the neonate, as for adults, must include support of the airway, breathing and circulation. Because of the unique physiology of a newborn infant, some aspects of drug therapy differ significantly from their counterparts in the resuscitation of adults, and hypoglycemia and hypothermia pose special threats to a distressed neonate. Epinephrine and atropine can be administered via an endotracheal tube, but vascular access, which is most easily obtained by cannulating an umbilical vessel, is required for administering other drugs. Initial drug therapy, including glucose, oxygen and bicarbonate, is intended to restore metabolic homeostasis. Bicarbonate administration must be preceded by adequate alveolar ventilation. Drugs used to increase cardiac output early in resuscitation include those that increase heart rate, increase preload or improve myocardial function. Other drugs used in extended intensive care may also improve cardiac output, alter the distribution of the circulation or alter pulmonary function or gas exchange. These agents will be reviewed in a subsequent article.

As for older children and adults, optimal resuscitation of a newborn infant requires both immediate cardiopulmonary resuscitation and ongoing intensive care, which have been joined within the concept of advanced cardiac life support.[1] The unique cardiopulmonary physiology of the neonate, however, dictates that the interventions that compose advanced life support for newborn infants must be chosen to meet the needs, capabilities and limitations of these patients, which may differ significantly from those of older patients. This is particularly true of drug therapies because many agents commonly used in resuscitation of adults have little application in infants, and some that are vital in neonates are not useful in older patients. In this two-part article, we review the general concepts of cardiopulmonary physiology and pharmacology relevant to neonatal resuscitation, with particular attention to those aspects of neonatal physiology that allow or demand modified pharmacologic management. In Part I we provide recommendations for drug therapy in imme-

diate resuscitation, as might be required in the delivery room. In Part II we address extended cardiopulmonary intensive care for neonates, which begins when a neonate is sufficiently stable to allow transfer to the intensive care nursery.

Fundamentals of Neonatal Resuscitation

Resuscitation of a distressed neonate requires orderly assessment and intervention, which should follow the same protocol regardless of the setting or cause of distress (Table 1). Resuscitation should begin by ensuring airway patency, by slight neck extension and jaw thrust or by endotracheal intubation. Breathing should be assisted if spontaneous respiration is inadequate, and external cardiac compressions should be started if the heart rate remains below 100 beats per minute. Drugs may be required if the infant's metabolic condition, gas exchange or cardiac output remain abnormal after these measures. The cardiac electrical rhythm (electrocardiogram) should be continuously monitored. If the infant is cyanotic, in

respiratory distress or requires cardiac compressions, 100% oxygen should be administered. Administering glucose may be lifesaving because hypoglycemic infants may be refractory to resuscitation efforts. Hypothermia increases metabolic requirements, impairs myocardial performance and increases vascular resistance, so resuscitation should be carried out under a radiant warmer whenever possible.

Drug Therapy

Drugs used in neonatal resuscitation may be classified as agents that (1) restore or maintain metabolic homeostasis, (2) increase cardiac output, (3) alter the distribution of the circulation or (4) alter pulmonary function or gas exchange. Part I of this review focuses on drugs in the first two categories. Additional agents in the second category and those in categories 3 and 4 will be discussed in Part II.

Routes of Administration

Although establishing vascular access must be given high priority, it is not essential for delivery of epinephrine[2] or atropine,[3] which are effective when delivered into an endotracheal tube. Other agents are best administered directly into the vascular system. In the first hours after birth, the umbilical vein can be quickly and easily cannulated by cutting the umbilical cord 0.5 to 1 cm from the abdominal wall and inserting a catheter into the single large flaccid vessel.[4] If the catheter can be advanced 10 cm into the vessel (6 to 8 cm in a premature infant), it has almost certainly transversed the ductus venosus into the vena cava or right atrium. If blood can be withdrawn freely, it is likely safe to administer drugs through the catheter.

Because passage of a catheter through the ductus venosus may be impossible after about 12 hours of age, an umbilical artery may need to be cannulated. This procedure is more time-consuming and requires greater skill, but also provides access for measuring blood pressure and sampling for blood gas determinations.[4] Administering catecholamines into arterial catheters may cause intense splanchnic, renal or peripheral vasoconstriction, so placing a peripheral or central venous catheter for administering these agents is mandatory. Because sick infants often have poor peripheral perfusion, cannulation of a peripheral vein may be extremely difficult. Venous cutdown or percutaneous cannulation of a central vein should be attempted only by skilled operators after another access route is established and the infant's condition is stable. If none of these routes can be readily secured, placement of a 16- or 18-gauge needle into the tibial or femoral marrow cavity will allow administration of fluids and drugs intraosseously.[5] Direct cardiac puncture is very hazardous and should be considered only as a last resort.

Agents That Restore Metabolic Homeostasis

Drugs that restore or maintain metabolic homeostasis, which either provide substrate for cellular metabolism or correct abnormalities that impair the capacity of the cells to utilize substrate, include glucose, oxygen and bicarbonate.

Glucose. With termination of transplacental glucose delivery at birth, the neonate becomes dependent on gluconeogenesis and mobilization of hepatic glycogen stores to maintain blood glucose levels. These stores are minimal at best in premature and small-for-gestational-age infants, and may be depleted by asphyxia, difficult or prolonged labor or in utero exposure to terbutaline or ritodrine. Infants of mothers with diabetes mellitus may be unable to mobilize hepatic glycogen, even though their stores are abundant. Glucose consumption is increased by hypoxia, hypothermia, hyperthermia and sepsis. These factors may account for the high incidence of hypoglycemia in neonates.[6]

Neonatal hypoglycemia may be asymptomatic or present with symptoms as varied as lethargy, hypotonia, seizures, impaired systemic perfusion, cyanosis or right-to-left shunting. The diagnosis requires early measurement of the blood glucose level using bedside test strips (Dextrostix or Chemstrip bG). If the blood glucose level is less than 40 mg per dl, intravenous administration of glucose (100 to 200 mg per kg or 1 to 2 ml per kg of dextrose solution 10% in water) is indicated. Larger doses may elicit exuberant insulin responses and cause severe rebound hypoglycemia, especially in infants whose mothers have diabetes. A continuous infusion of glucose at 6 to 8 mg per kg per minute should be started immediately. Infants of mothers with diabetes may require more rapid infusions (8 to 10 mg per kg per minute). Euglycemia may be achieved more rapidly in infants with adequate hepatic glycogen stores after intravenous administration of glucagon (300 µg per kg), but this is unlikely to benefit most hypoglycemic neonates. The blood glucose level must be measured frequently until stable euglycemia is documented; additional doses of glucose (100 mg per kg per dose) or an increased rate of infusion may be required.

Oxygen. Tissue hypoxia can be categorized according to its physiologic basis, as shown in Table 2. Most hypoxic

TABLE 1.—*The ABCs of Neonatal Resuscitation*

Airway	Electrocardiogram
Breathing	F_1O_2
Circulation	Glucose
Drugs	Heat

F_1O_2 = fraction of inspired oxygen

TABLE 2.—*Physiologic Classification of Hypoxic Conditions*

Group	I	II	III	IV
Physiologic Category	Hypotonic Hypoxemia	Normotonic Hypoxemia	Hypodynamic Hypoxia	Histotoxic Hypoxia
Arterial O_2 tension	↓	↔	↔	↔
Arterial O_2 content ...	↓	↓	↔	↔
Arterial O_2 saturation ..	↓	↔	↔	↔
O_2 carrying capacity	↔	↓	↔	↔
Mixed venous O_2 saturation ..	↓	↓	↓	↑
Cardiac output	↔,↑	↑	↓	↔,↑
Tissue O_2 use ...	↓,↔	↓,↔	↓,↔	↓

↓ = decreased; ↑ = increased; ↔ = unchanged

infants have hypotonic hypoxia, which is apparent as cyanosis and reduced arterial oxygen tensions. Infants with normotonic hypoxemia have severe anemia and should be transfused with erythrocytes. Infants with hypodynamic hypoxia, resulting from impaired cardiac output, may also be cyanotic but primarily have signs of poor systemic perfusion, as described below. The management of such infants is the subject of much of this review. Histotoxic hypoxia in neonates, resulting from the inability of cells to use oxygen, most often is due to severe asphyxia or overwhelming sepsis and rarely is treatable.

Administering oxygen may ameliorate tissue hypoxia in many of these conditions, but is consistently effective only for hypotonic hypoxemia (group I, Table 2). Within this category, hypoxemia due to ventilation-perfusion mismatching (pneumonia, aspiration) or impaired diffusion capacity (retained fluid, respiratory distress syndrome) may abate by administering supplemental oxygen only. Assisted ventilation should be provided for hypoxemia due to hypoventilation, even though the arterial oxygen pressure (Pao_2) is improved by oxygen administration. Administering oxygen is of no benefit for hypoxemia due to fixed right-to-left shunting, as in infants with cyanotic congenital heart disease, but oxygen-induced dilation of the pulmonary arteries may result in pronounced abatement of hypoxemia due to dynamic right-to-left shunting through fetal channels, as in infants with persistent pulmonary hypertension or severe pulmonary parenchymal disease.

Until the nature of hypoxia is delineated, it is appropriate to administer oxygen, in concentrations sufficient to relieve or eliminate signs of distress, to any infant with cyanosis or respiratory distress. Arterial blood gas measurements should guide subsequent adjustments of the fractional concentration of inspired oxygen (F_1o_2) to achieve the desired Pao_2, which may range from 50 to 60 mm of mercury for a small premature infant to 100 to 120 mm of mercury for a term infant with persistent pulmonary hypertension. If hypoxemia persists during administration of 100% oxygen, continuous positive airway pressure or assisted ventilation should be initiated; the Pao_2 usually increases in infants with pulmonary disease, but falls or is unchanged in those with congenital heart disease. Comparison of preductal (right radial artery) and postductal (umbilical artery) arterial oxygen tensions and assessment of the response to hyperventilation (to achieve an arterial carbon dioxide pressure [$Paco_2$] below 30 mm of mercury) should be done in persistently hypoxemic infants to distinguish those with cyanotic heart disease from those with pulmonary hypertension.[7] Failure to respond to oxygen administration may also result from mechanical problems in the delivery system, such as kinked tubing, air entrainment or disconnection of the oxygen source.

The use of oxygen has been implicated in causing bronchopulmonary dysplasia, adult respiratory distress syndrome and retinopathy of prematurity. These potential complications of oxygen therapy clearly require titration of the F_1o_2 to the minimum level compatible with adequate arterial oxygenation, but do not justify withholding oxygen from any distressed infant.

Bicarbonate. Acidemia has numerous detrimental effects, including impaired myocardial function, increased systemic and pulmonary vascular resistances, reduced responsiveness to catecholamines and inhibition of oxidative glucose metabolism. Correction of acidemia reverses these effects, resulting in improved cardiac output, tissue perfusion and substrate utilization.

Acidemia in a neonate is usually respiratory in origin and can be rapidly corrected by assisted ventilation. Modest metabolic acidosis may result from lactic acid production during paroxysmal events, such as intrapartum asphyxia, aspiration or cardiac arrest. Effective resuscitation, including ventilation and restoration of systemic perfusion, allows hepatic conversion of lactate mobilized from tissues to bicarbonate, restoring the serum bicarbonate to normal levels. Unless the pH is less than 7.2, bicarbonate administration is usually unnecessary. Persistent metabolic acidosis should suggest inadequate delivery of substrate, such as oxygen, to tissues (decreased cardiac output, severe anemia), histotoxic hypoxia (sepsis, severe asphyxia), localized tissue infarction (necrotizing enterocolitis, intracranial hemorrhage) or inborn errors of metabolism. In these conditions, bicarbonate therapy is only a temporizing measure, which may allow survival until specific therapy is effective.

The physiologic efficacy of bicarbonate, which is a relatively weak chemical pH buffer, depends on the volatile nature of the acid moiety (CO_2) in the buffer reaction:

$$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2.$$
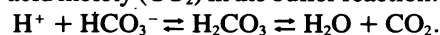
It should be emphasized that the blood pH will not increase and the cerebrospinal fluid pH will *decrease*[8] after bicarbonate administration unless adequate alveolar ventilation ensures excretion of the carbon dioxide generated by the buffer reaction. Thus, bicarbonate administration is contraindicated by inadequate alveolar ventilation.[9] Tromethamine (THAM), an effective buffer near physiologic pH that does not require excretion of volatile acid, can be used in infants for whom adequate ventilation cannot be established. This buffer has no advantage over bicarbonate for hypernatremic infants because both buffers contain 2 mosm per mEq of buffering capacity.

During cardiorespiratory arrest or following severe asphyxia, bicarbonate may be given empirically in a dose of 1 mEq per kg, followed by additional doses of 0.5 to 1 mEq per kg about every ten minutes. As soon as possible, doses should be determined by blood gas values, using the formula:

HCO_3^- dose (mEq) = 0.25 × base deficit (mEq per liter)
× body weight (kg).

Excessive doses, including correction of the pH to 7.4 early in resuscitation (which will be followed by mobilization of bicarbonate-precursor organic acids from tissues), will cause metabolic alkalosis, impairing both oxygen unloading from hemoglobin and release of endogenous catecholamines. To prevent hypernatremia or hyperosmolality following doses of bicarbonate exceeding 0.5 mEq per kg per hour, sufficient free water must be provided to allow renal excretion of the solute load, requiring that the net solute content of administered fluids is no greater than that of one-half isotonic saline solution. Hypokalemia and reduced ionized calcium levels also may result from bicarbonate administration. Rapid infusion of hypertonic solutions may predispose to intracranial hemorrhage,[10] so each dose should be infused over five to ten minutes and the concentration should never exceed 0.5 mEq per ml (1,000 mosm per liter). Bicarbonate inactivates catecholamines and precipitates if admixed with calcium salts.

Agents That Increase Cardiac Output

Cardiac output is determined by the cardiac rate and rhythm (chronotropy), ventricular end-diastolic volume (preload), myocardial contractility (inotropy) and the vascular resistance (afterload). Estimating cardiac output in the neonate depends heavily on clinical assessment because measurement by thermodilution techniques is extremely unreliable. Doppler echocardiography[11] provides more reliable estimates of cardiac output in a sick infant. Decreased cardiac output with impaired systemic perfusion is suggested by pallor, mottling, prolonged capillary filling times (greater than three to four seconds) and cool or cyanotic extremities. These findings may not be present in infants of gestational age less than about 28 weeks because of immature autonomic regulation of vascular tone. Urine output in excess of 1 ml per kg per hour suggests adequate cardiac output and renal perfusion. Urine sodium concentrations of less than 10 to 15 mEq per liter (20 mEq per liter in a premature infant) or a fractional sodium excretion of less than 1% suggests that renal perfusion or intravascular volume is inadequate. Adequate urine flow and sodium excretion may also reflect renal immaturity or acute renal failure, however. Metabolic acidosis is a sign of severely compromised cardiac output.

Agents That Increase Heart Rate

Because cardiac output in a normal neonate depends primarily on the heart rate,[12] interventions intended to increase cardiac output must begin with establishment of an adequate heart rate (120 to 160 beats per minute in term infants or 140 to 180 beats per minute in preterm infants). In some infants, a rate of 200 beats per minute may be required. Bradycardia in a newborn infant is most frequently due to inadequate ventilation and rapidly resolves with effective assisted breathing. Persistent bradycardia with adequate ventilation may result from severe myocardial injury (following profound asphyxia, for example), congenital heart block (due to congenital cardiac malformations or maternal lupus erythematosus) or pronounced vagal effects (visceral distension or central nervous system injury).

Epinephrine. Epinephrine, which has both β- and α-adrenergic effects,[13] remains the primary agent for managing bradycardia in a neonate. α-Adrenergic effects increase systemic vascular resistance, systolic and diastolic blood pressures and myocardial perfusion. β-Adrenergic effects increase myocardial irritability, rhythmicity and contractility, resulting in increased heart rate and cardiac output. Intravenous or intratracheal administration of epinephrine (0.1 ml per kg of 1:10,000 solution) is indicated for infants with bradycardia or asystole and may help restore myocardial contractility in infants with electromechanical dissociation. This dose may be repeated every three to five minutes until an adequate cardiac rhythm is obtained. If repeated doses are required to maintain a heart rate of greater than 120, isoproterenol infusion should be initiated. A continuous infusion of epinephrine (0.1 to 1 μg per kg per minute) may be preferable for infants for whom α-adrenergic effects are required to maintain systemic arterial pressures.

Epinephrine is ineffective if the systemic pH is less than 7.1 and is inactivated by admixture with alkaline solutions. Myocardial stimulation may cause pathologic tachyarrhythmias. Excessive doses may impair renal, splanchnic or pe-

ripheral perfusion, and extravasation or intramyocardial injection may cause local tissue necrosis.

Isoproterenol. Isoproterenol, a pure β-adrenergic agonist, increases myocardial irritability, rhythmicity and contractility and causes peripheral vasodilation and relaxation of bronchial and visceral smooth muscle.[13] Because the chronotropic (rate increasing) effects are prominent (relative to other β-specific catecholamines), it is particularly useful for the management of bradycardia with minimally compromised myocardial contractility. Continuous infusion of isoproterenol (0.1 to 1.5 μg per kg per minute, titrated to achieve the desired heart rate) is indicated for second- or third-degree heart block, bradycardia from other causes and asystole. Complications of isoproterenol infusion are similar to those of epinephrine, but β_2-adrenergic-mediated vasodilation, which is not balanced by α-adrenergic effects, may cause hypotension even though cardiac output is increased.

Atropine. The vagolytic effects of atropine are mediated by peripheral blockade of the muscarinic effects of acetylcholine. The effects of atropine therefore depend on the degree of vagal stimulation present before its administration. Because autonomic innervation of the viscera and central control of the autonomic nervous system mature significantly during the latter half of gestation,[14] it might be expected that atropine would be more effective in term than in preterm infants. Because autonomic nervous control is poorly integrated in the premature infant, however, modest visceral stimuli, such as distension of the stomach, bladder or rectum, may elicit excessive vagotonic responses and precipitate profound bradycardia, which is rapidly corrected by atropine.[15] The use of atropine (0.01 to 0.04 mg per kg per dose every two to five minutes) is also indicated for bradycardia that compromises cardiac output or second- or third-degree heart block, and it may be effective for asystole refractory to epinephrine and calcium. Cumulative doses in excess of 0.1 mg per kg are unlikely to be of additional benefit, but are likely to produce central nervous system signs of atropine intoxication, including hyperthermia. In therapeutic doses, atropine will increase myocardial oxygen consumption and may cause tachyarrhythmias.

Cardioversion and defibrillation. Electrical stimulation with 1 to 2 watt-second per kg using pediatric paddles may restore a normal cardiac rhythm in infants with ventricular fibrillation, ventricular tachycardia or asystole. Most neonates with these serious arrhythmias have sustained overwhelming cerebral as well as cardiac injury, so this therapy is rarely indicated or effective.

Agents That Increase Preload

Because the cardiac ventricles are much less compliant in infants than in adults,[16] the relationship between end-diastolic filling pressures and ventricular volume (preload) is less direct in the neonate, and increased cardiac output after expansion of the vascular volume is less consistent. Nonetheless, hypovolemia, which may result from external blood losses (such as fetomaternal bleeding, fetoplacental transfusion or placenta or vasa previa), internal bleeding (intracranial, adrenal or hepatic hematomas) or third-space losses (postasphyxial, sepsis, hydrops), is a common cause of poor cardiac output in a neonate.

Assessment of preload depends primarily on invasive

measurement of end-diastolic filling pressures, which is most readily achieved by catheterization of the umbilical vein. Because these catheters may enter the left atrium as well as the right, the position of the catheter tip must be determined radiographically, by ultrasonography or by measurement of the venous oxygen saturation, so that transduced pressures can be appropriately interpreted. In a normal infant, the mean central venous or right atrial pressure is 1 to 7 mm of mercury and the mean left atrial pressure is 10 to 13 mm of mercury;[17] end-diastolic pressures are slightly lower. Central venous pressures as high as 8 to 10 mm of mercury or left atrial pressures of 12 to 15 mm of mercury may be required to achieve optimal cardiac output in a sick infant, however. Lower pressures suggest relative hypovolemia, but low left atrial pressures may also reflect high pulmonary vascular resistance. Elevated filling pressures may result from relative hypervolemia, impaired ability of the ventricles to accommodate the venous return (reduced ventricular compliance, tamponade) or reduced ventricular pumping capacity (decreased contractility). The most useful information is obtained by measuring the venous pressure before and after expansion of the vascular volume. A sustained elevation in the central venous or left atrial pressure following administration of 5 to 10 ml per kg of plasma or blood effectively rules out hypovolemia. If the venous pressure rises transiently or is not affected, hypovolemia should be suspected. Occasionally venous or arterial pressures (or both) fall after administration of volume expanders; this usually results from decreased sympathetic nervous system-mediated vascular tone and indicates significant relative hypovolemia. If there is an apparent improvement in cardiac output, the venous pressure at which improvement occurs can be used to guide subsequent administration of volume expanders. The filling pressures at which cardiac output appears to be optimal must be reassessed at least twice a day.

Crystalloid solutions. Normal saline and lactated Ringer's solutions are readily available, inexpensive and well tolerated when used empirically. These isotonic solutions are distributed into the entire extracellular space, so that relatively large volumes (at least 20 ml per kg) must be given to achieve significant expansion of the vascular volume, potentially exacerbating peripheral and pulmonary edema. Hypernatremia (potentially increasing the risk of intraventricular hemorrhage) or hypervolemia (predisposing to patency of the ductus arteriosus) may result from the unpredictable metabolism of fluid and electrolytes in a sick or premature infant. Metabolic acidosis with an elevated anion gap may follow administration of lactate or acetate, which may not be metabolized to bicarbonate in infants with impaired hepatic function or perfusion. Nonetheless, isotonic crystalloid solutions (10 ml per kg over 30 to 60 minutes) are preferred for volume expansion in modestly ill infants with poor urine output. If urine output does not improve and hypovolemia has been ruled out, adverse consequences of crystalloid administration may be reduced by administering a diuretic.

Colloid solutions. Albumin and plasma protein fraction are readily available and easily stored. They distribute primarily into the vascular space and may increase plasma protein levels, but these effects are short-lived. Distribution of protein from these solutions into the extravascular space contributes to peripheral and pulmonary edema,[18] which may be

difficult to mobilize. These products are expensive and they should be used only if there is a clear indication for colloid rather than crystalloid solutions. Fresh frozen plasma is preferred because it contains more high-molecular-weight components, which may be better retained within the vascular space, as well as immunoglobulins, complement and clotting factors.

Blood products. Packed erythrocytes and fresh frozen plasma are the products of choice for vascular volume expansion in a critically ill infant. Cytomegalovirus-seronegative, type specific or type O, Rh-negative blood crossmatched against the mother's is ideal and should be available if delivery of a severely ill infant is anticipated. Uncrossmatched type O, Rh-negative blood can be used in emergencies, but transfusion reactions will occasionally occur. An infusion of 10 ml per kg of plasma (if the hematocrit is greater than 60%) or erythrocytes (if the hematocrit is less than 40%) over 15 to 30 minutes should be followed immediately by reassessment of the infant's hemodynamic condition. Repeated doses to volumes approximating the patient's blood volume (80 to 100 ml per kg) may be required to achieve normovolemia. Rapid infusions should be avoided because sudden changes in the vascular volume may cause intracranial hemorrhage.

Agents That Enhance Myocardial Function

There are many causes of impaired myocardial function in a neonate. Acute injury resulting from asphyxia or sepsis (especially due to group B *Streptococcus,* which produces a cardiotoxin) is most common. Metabolic derangements, including acidemia, hypoglycemia and hypocalcemia, are also frequent. Intrinsic disorders of the myocardium, such as hypertrophic cardiomyopathy (common in infants of diabetic mothers) or myocardial edema (as in hydrops fetalis), are less common, but more difficult to treat.

Calcium. Transient hypoparathyroidism occurs in most infants in the first days of life and is more severe and prolonged in premature infants and infants of diabetic mothers. Premature infants also have persistently reduced total body calcium stores because extrauterine calcium acquisition occurs much more slowly than transplacental calcium transfer. Calcium stores may be further depleted by furosemide administration, which causes hypercalciuria. Total serum calcium levels as low as 7.5 mg per dl (7.0 in a premature infant) may be normal and, because of the relatively low plasma protein levels of neonates, are usually associated with normal ionized calcium levels. Complexing of calcium by citrate and phosphate after administration of large volumes of blood products (as with exchange transfusion, massive hemorrhage or capillary leak syndromes) may result in reduced ionized calcium to levels sufficient to cause electromechanical dissociation, even though the total serum calcium level may be normal.

Calcium was initially used in cardiopulmonary resuscitation because of its crucial role in coupling electrical and mechanical events within the myocardium. Recent experience with calcium channel blockers has raised doubts regarding both the efficacy and safety of calcium in resuscitating adults because vasoconstriction resulting from increased ionized calcium levels may further compromise perfusion of already ischemic tissues, contributing to cardiac, cerebral or intestinal injury. In a hypocalcemic premature infant, however, calcium administration results in increased heart rate, myo-

cardial contractility and blood pressure.[19,20] Catecholamine release from the adrenals, which may be a critical factor in the survival of infants in shock, may also require calcium. Calcium is indicated for any hypocalcemic infant and may be beneficial for infants with compromised myocardial function or cardiac arrest. It is also indicated for electromechanical dissociation, which should be suspected in any infant with a normal electrical cardiac rhythm, elevated central venous pressure and reduced systemic arterial mean and pulse pressures. Pericardial tamponade must also be ruled out.

Calcium chloride (20 mg per kg per dose, given intravenously over several minutes) is the preferred salt for use in emergency situations, such as cardiac arrest, electromechanical dissociation or severe hypotension attributable to poor cardiac contractility, because it is virtually completely dissociated in solution, making more ionized calcium immediately available. This dose can be repeated every ten minutes as required. Extravasation of calcium chloride results in rapid tissue necrosis, so calcium gluconate (50 to 100 mg per kg every four to six hours), which is much less toxic to tissues, should be given in all nonemergency circumstances.

Summary

In this review, we have provided recommendations for pharmacologic therapy during the initial phases of resuscitation of a newborn infant, as might be required in the delivery room. In this process, attention must be given to basic resuscitation (airway, breathing and circulation) before drug therapy can be initiated to restore metabolic homeostasis and improve cardiac output. Cardiac output in a neonate is strongly dependent on heart rate, requiring prompt treatment of bradycardia with epinephrine, isoproterenol or atropine, or a combination of these drugs. Hypovolemia must also be corrected expeditiously. Calcium should be given if myocardial performance is compromised. If effective, these measures should result in a sufficiently stable condition in the infant to allow transfer to the intensive care nursery where extended intensive care, to be discussed in Part II of this series, can be initiated. These recommendations are based on our accumulated experience with application of current knowledge of neonatal physiology and pharmacology and can be expected to change as new information allows further refinement of these clinical strategies.

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